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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/334,325
Filing Date: June 16, 1999
Appellant(s): CEDERHOLM-WILLIAMS, STEWART A.

John M. Kilcoyne
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7-20-06 appealing from the Office action mailed 2-22-06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 13-16 are directed to a method of transforming a cell *in vitro* or *in vivo* by applying, in order, a nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, to the cell, a pliable and adhesive fibrin gel to the cell so a to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell. Claim 15 specifies the pliable, adhesive fibrin gel is formed by mixing a fibrin monomer composition with a polymerizing agent and the cell is contacted with the mixture while the mixture is pliable and adhesive. Claim 16 specifies the fibrin monomer composition comprises acid-solubilized fibrin and the polymerizing agent comprises a base effective to neutralize the mixture to form fibrin polymer.

The specification discusses advantages of fibrin monomer-based sealants over fibrinogen-based sealants and discloses the preparation of preferred sealant compositions and the incorporation of nucleic acid into fibrin gel, and spraying of transforming composition comprising nucleic acids, fibrin monomer preparation, and polymerizing agent to site of delivery so that these three components can converge and mix. The claims are directed to a method of transforming a cell *in vitro* and *in vivo* via various administration routes. The claims read on applying a nucleic acid to a cell first and then applying a pliable, adhesive fibrin gel to said cell

so as to transform the cell *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc., via various administration routes.

The specification fails to provide adequate guidance and evidence for transforming a cell *in vitro* or *in vivo* by applying a nucleic acid, such as a vector or a virus carrying the nucleic acid, to the cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vitro* or *in vivo* at any location of any subject via various administration routes. The specification merely states that "the TC can be applied to cells or tissue, and the sealant can be applied to fix the TC in place" (see specification, p. 17, lines 28-29). No working example or evidence has been provided in the specification in regard to how the cells are transformed by the claimed method and whether the cells are transformed *in vitro* or *in vivo* via various administration routes. The mechanism of the cell transformation by the claimed method was unknown at the time of the invention.

The specification teaches compositions of fibrin sealants that incorporate recombinant vectors for delivery to a tissue or cell, and "[B]y use of such compositions, the vectors can be maintained at a locally at high concentration in the solid gel produced by the sealant, thereby increasing the efficiency of transfection or transformation of cells (see specification, p. 2, lines 9-13). The orderly method steps of (1) applying a nucleic acid to the cell and then (2) adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of nucleic acid in the fibrin gel adhered to the cell as instantly claimed, must provide such a high concentration of the vector in order to increase the efficiency of the transformation of the cells *in vitro* or *in vivo* in the claimed invention. The state of the art of using fibrin gel for delivering nucleic acid is such that the nucleic acid solution is mixed with fibrin monomer or fibrinogen

first, then the fibrin gel is polymerized before being delivered to the target site. Donovan, 1998 (US Patent No. 5,833,651) constructs plasmid CMVhpAP expressing the reporter hpAP gene under the control of CMV promoter and an E1 deleted recombinant adenoviral vector ADVhpAP expressing hpAp, and prepared a fibrin covered stent which was placed in a solution of plasmid or virus overnight to load the plasmid or virus into the fibrin covered stent for determining whether fibrin enhances gene delivery to the artery (e.g. column 18, 19, 20). Donovan further teaches mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell (e.g. column 13). Schek et al., 2003 (Molecular Therapy, Vol. 9, No. 1, p. 130-138) teaches mixing adenoviral particles with fibrinogen solution in vitro, gelation of the fibrinogen by adding thrombin to form hydrogel, and implanting the hydrogel to immunocompromised mice (e.g. p. 137, left column). Schek shows that fibrin hydrogel exhibits a threefold extension of bioactivity of the virus delivered as compared to virus without hydrogel and suggests hydrogel may be used as carrier to control delivery of the virus and resultant tissue regeneration (e.g. abstract). In other words, the art of record only teaches pre-mixing fibrin with nucleic acid resulting in the nucleic acid being trapped in the fibrin gel for the method to work. The specification as filed also teaches the same (see p. 2, lines 9-13, p. 17, lines 8-17, lines 27-28). Therefore, neither the art nor the specification teaches where the nucleic acid is first applied to the cells followed by application of fibrin so as to transform cells with increased transformation efficiency. There is no evidence of record that shows increased or enhanced efficiency of cell transformation by the claimed method either in vitro or in vivo via various administration routes. When the nucleic acid is first applied to the cells followed by application of fibrin, the specification fails to provide any specific

guidance as to how one skilled artisan would have first applied nucleic acid to the cells and subsequently applied fibrin in vitro or in vivo to the same cells so as to trap effective amount of nucleic acid to transform the cells with said nucleic acid. Since the mechanism of cell transformation by the claimed method was unknown at the time of the invention and the lack of working example and evidence of record regarding the claimed method, one skilled in the art would not know how to increase or enhance the efficiency of cell transformation *in vitro* or *in vivo* by using the claimed method and would require undue experimentation to practice over the full scope of the invention claimed.

Further, the claims encompass transforming cells in vivo via various administration routes, such as intravenous administration, intraperitoneal administration, oral administration, subcutaneous administration, and intramuscular administration etc. The specification fails to provide adequate guidance and evidence for how to apply nucleic acid to the cell first and then administer a pliable, adhesive fibrin gel to the cells at various locations of a subject via various administration routes such that the cells at the target site of the subject would have increased or enhanced transformation efficiency as compared to other method, such as the method known in the art by mixing the nucleic acid solution and the fibrin monomer together before administration to the cells. The specification fails to demonstrate how intravenous administration, oral administration, intraperitoneal administration or subcutaneous administration could deliver the pliable, adhesive fibrin gel to the cells of kidney, pancreas, heart, stomach, colon, liver, intestine, or brain and the pliable, adhesive fibrin gel would not polymerize before reaching the target cells in vivo. The lack of teachings and evidence of record for such delivery of the pliable, adhesive

fibrin gel in vivo would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

The specification also fails to provide adequate guidance and evidence for how to administer a pliable, adhesive fibrin gel to a cell having administered nucleic acid in a subject such that target cells in said subject are transformed with said nucleic acid. The specification fails to provide adequate guidance for how to deliver the pliable, adhesive fibrin gel before the fibrin gel is polymerized to target cells in a subject via various administration routes for transformation of said cells with increased efficiency. It was known in the art that the pliable, adhesive fibrin gel will polymerize quickly. The specification states that "Generally, the sealant mixture remains conveniently pliable for about 30 seconds or less"(page 17, lines 16, 17). Since the pliable, adhesive fibrin gel will polymerize in a short period of time, one would need to deliver said fibrin gel to target cells at various locations in a subject before polymerization of said fibrin gel so as to increase transform efficiency of said target cells with a nucleic acid. This would be problematic because there is not much time for one skilled in the art to deliver the pliable and adhesive fibrin gel to the target cells inside the body of the subject, such as cells in liver, kidney, pancreas, heart, colon, intestine, stomach etc, before the pliable and adhesive fibrin gel is polymerized. When the pliable and adhesive fibrin gel is polymerized before it reaches the target cells, the nucleic acid on the cells would not be entrapped in the fibrin gel and the target cells would not be transformed with said nucleic acid or with increased transformation efficiency as compared to other methods, such as mixing the nucleic acid and the fibrin monomer before administration. There is no evidence of record that shows transformation of target cells increased transformation efficiency of target cells in a subject with any nucleic acid via

administering the nucleic acid to the cells first and then administering the pliable and adhesive fibrin gel to said cells.

The claims read on applying a nucleic acid to cells in vivo so as to transform cells and the transformation of cells in vivo must have a use, which is to provide therapeutic effect in vivo. The title of the present invention reads "Fibrin sealant as a transfection /transformation vehicle for gene therapy". Therefore, the claims read on gene therapy in vivo. The state of the art for gene therapy *in vivo* was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate resolution of the problem of vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and

to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). These arts emphasize the unpredictability of the state of the art of gene therapy in general and in view of the lack of any specific guidance and evidence in the specification as to how to deliver nucleic acid and fibrin to the same cell in sufficient amounts so as to increase transformation efficiency, when the nucleic acid is applied first followed by fibrin a skiled artisan would have required extensive experimentation to practice over the full scope of the

invention claimed. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to transform a cell *in vivo* with any nucleic acid and a pliable, adhesive fibrin gel via various administration routes so as to provide therapeutic effects in an individual for a particular disease or disorder.

The quantity of experimentation needed to make or use the present invention includes trail and error experimentation to elucidate the mechanism of cell transformation *in vitro* or *in vivo* by applying nucleic acid to cells first, then administering a pliable, adhesive fibrin gel to said cells, trial and error experimentation to determine how to increase or enhance cell transformation efficiency *in vitro* and *in vivo* by the claimed method, trial and error experimentation to determine how to administer a nucleic acid to the target cell on the surface of a subject or to the target cell at various locations inside the body of a subject, such as liver, kidney, lung, intestine, stomach etc., trial and error experimentation to determine how to administer the pliable and adhesive fibrin gel to the target cell on the surface of a subject or to the target cell at various locations inside the body of a subject, such as liver, kidney, lung, intestine, stomach etc., via various administration routes before the fibrin gel get polymerized so as to transform the target cell with said nucleic acid or to increase cell transformation efficiency, and trial and error experimentation to transform target cells with the claimed method such that therapeutic effects can be obtained for a particular disease or disorder *in vivo*.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which

is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

(10) Response to Argument

Appellant argues that the 35 U.S.C. 112 first rejection is simply a rejection under 35 U.S.C. 101 in the guise of a rejection under 35 U.S.C. 112 (brief, p. 3). This is not found persuasive because of the reasons of record. The present rejection is 35 U.S.C. 112 first paragraph enablement rejection but NOT a 35 U.S.C. 101 rejection. Examiner is confused how this enablement rejection is a 35 U.S.C. 101 rejection under the guise of a rejection under 35 U.S.C. 112.

Appellant argues that in previous rejection, the Office acknowledged that transforming a cell in vivo was enabled when done with a stent or balloon catheter and transforming a cell in vitro was enabled (brief, p. 3-4). This is not found persuasive because of the reasons of record and the following reasons. Firstly, the Office acknowledged that transforming a cell in vivo was enabled as disclosed by the cited reference Donavan et al., 1998 (US Patent 5,833,651) (see Office action mailed 3-12-03, p. 4). The scope of the claims at that time was broader than that of the claims in the instant brief, i.e. the claims at that time encompass any order or combination of adding the nucleic acid and the pliable, adhesive fibrin gel to the cells. Donovan teaches preparing a fibrin covered stent and the stent was placed in a solution of plasmid or virus overnight to load the plasmid or virus into the fibrin covered stent for determining whether fibrin enhances gene delivery to the artery. Donovan also teaches mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell. Donavan does not teach applying nucleic acid to a cell first then adhering a

pliable, adhesive fibrin gel to the cell so as to trap the nucleic acid in the fibrin gel adhered to the cell and transforming the cell with the nucleic acid. The method as taught by Donavan to transform a cell in vivo is enabled, however, the method to transform a cell in vivo as claimed in the instant invention, which is different from the method taught by Donavan and by the state of the art, is not enabled.

Secondly, with regard the enablement issue of transforming a cell in vitro with the claimed method of instant invention, the state of the art of using fibrin gel for delivering nucleic acid is such that the nucleic acid solution is mixed with fibrin monomer or fibrinogen first, then the fibrin gel is polymerized before being delivered to the target site, or the fibrin gel is formed first, then the nucleic acid is added to said fibrin gel before applying to target cell. In other words, the art of record only teaches pre-mixing fibrin with nucleic acid resulting in the nucleic acid being trapped in the fibrin gel for the method to work. The specification as filed also teaches the same (see p. 2, lines 9-13, p. 17, lines 8-17, lines 27-28). Therefore, neither the art nor the specification teaches where the nucleic acid is first applied to the cells followed by application of fibrin so as to transform cells with increased transformation efficiency. There is no evidence of record that shows increased or enhanced efficiency of cell transformation by the claimed method either in vitro or in vivo via various administration routes. When the nucleic acid is first applied to the cells followed by application of fibrin, the specification fails to provide any specific guidance as to how one skilled artisan would have first applied nucleic acid to the cells and subsequently applied fibrin in vitro or in vivo to the same cells so as to trap effective amount of nucleic acid to transform the cells with said nucleic acid. Thus, the claimed method of transforming a cell in vitro is not enabled.

Appellant argues that there is no requirement of the patent law to explain or elucidate the mechanism of cell transformation (brief, p. 4, first paragraph). This is not found persuasive because of the reasons of record and the following reasons. Indeed, it is not necessary to disclose the mechanism of cell transformation, however, it is required to disclose sufficient enabling disclosure for the claimed invention and the specification of the instant invention fails to do so. As discussed above, the state of the art of using fibrin gel for delivering nucleic acid is such that the nucleic acid solution is mixed with fibrin monomer or fibrinogen first, then the fibrin gel is polymerized before being delivered to the target site, or the fibrin gel is formed first, then the nucleic acid is added to said fibrin gel before applying to target cell, which is different from the invention claimed in the instant application. The claims are directed to a method of transforming a cell *in vitro* and *in vivo* via various administration routes, and encompass applying a nucleic acid to a cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc., via various administration routes. The specification fails to provide adequate guidance and evidence for transforming a cell *in vitro* or *in vivo* by applying a nucleic acid, such as a vector or a virus carrying the nucleic acid, to the cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vitro* or *in vivo* at any location of any subject via various administration routes. There is no evidence of record that shows cell transformation or increased or enhanced efficiency of cell transformation by the claimed method either in vitro or in vivo via various administration routes. When the nucleic acid is first applied to the cells followed by application of fibrin, the specification fails to provide any specific guidance as to how one skilled artisan would have first

applied nucleic acid to the cells and subsequently applied fibrin in vitro or in vivo to the same cells so as to trap effective amount of nucleic acid to transform the cells with said nucleic acid. It is unclear how intravenous administration, oral administration, intraperitoneal administration or subcutaneous administration etc. could deliver the pliable, adhesive fibrin gel to the cells of kidney, pancreas, heart, stomach, colon, liver, intestine, or brain etc. and the pliable, adhesive fibrin gel would not polymerize before reaching the target cells in vivo. It was known in the art that the pliable, adhesive fibrin gel will polymerize quickly. There is no evidence that shows cell transformation by applying a nucleic acid to a cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vitro* or *in vivo* at any location of any subject via various administration routes. The lack of teachings and evidence of record for such delivery of the pliable, adhesive fibrin gel would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Appellant argues that it is not required to "increase or enhance cell transformation efficiency" by the patent law (brief, p. 4, second paragraph). This is not found persuasive because of the reasons of record and the following reasons. Indeed, it is not required to "increase or enhance cell transformation efficiency". However, the specification teaches compositions of fibrin sealants that incorporate recombinant vectors for delivery to a tissue or cell, and "[B]y use of such compositions, the vectors can be maintained at a locally at high concentration in the solid gel produced by the sealant, thereby increasing the efficiency of transfection or transformation of cells (see specification, p. 2, lines 9-13). The orderly method steps of (1) applying a nucleic acid to the cell and then (2) adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of nucleic acid in the fibrin gel adhered to the cell as instantly

claimed, must provide such a high concentration of the vector in order to increase the efficiency of the transformation of the cells *in vitro* or *in vivo* in the claimed invention. Thus, increasing the efficiency of transfection or transformation of cells appears to be the purpose of using the compositions of fibrin sealants that incorporate recombinant vectors for delivery to a tissue or cell. Even without the purpose of increasing or enhancing the efficiency of cell transformation, the specification also fails to provide adequate guidance and evidence for how to transform a cell in vitro or in vivo via various administration routes by using the claimed method. The art of record only teaches pre-mixing fibrin with nucleic acid resulting in the nucleic acid being trapped in the fibrin gel for the method to work. The specification as filed also teaches the same (see p. 2, lines 9-13, p. 17, lines 8-17, lines 27-28). Therefore, neither the art nor the specification teaches where the nucleic acid is first applied to the cells followed by application of fibrin so as to transform cells with increased transformation efficiency. There is no evidence of record that shows cell transformation or increased or enhanced efficiency of cell transformation by the claimed method either in vitro or in vivo via various administration routes. When the nucleic acid is first applied to the cells followed by application of fibrin, the specification fails to provide any specific guidance as to how one skilled artisan would have first applied nucleic acid to the cells and subsequently applied fibrin in vitro or in vivo to the same cells so as to trap effective amount of nucleic acid to transform the cells with said nucleic acid. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Appellant argues that it is not required by the patent law to show every possible way to administer his invention (brief, p. 4, third paragraph). This is not found persuasive because of

the reasons of record and the following reasons. The claims encompass applying a nucleic acid to a cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc., via various administration routes. Those various administration routes includes intravenous administration, intraperitoneal administration, oral administration, topical administration, subcutaneous administration, and intramuscular administration etc. The specification fails to provide adequate guidance and evidence for how to apply nucleic acid to the cell first and then administer a pliable, adhesive fibrin gel to the cells at various locations of a subject via various administration routes such that the cells at the target site of the subject are transformed with the nucleic acid. The specification fails to provide sufficient enabling disclosure for the claimed invention. Therefore, the claims are not enabled as claimed.

In conclusion, each of the claims 1 and 13-16 are properly rejected under 35 U.S.C. 112 first paragraph for the reasons discussed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Shin-Lin Chen

s/Chen

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